Modelling the calcium-induced periodic and anisotropic contraction of cardiac myocytes

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Introduction

Since the pioneering work of Fabiato and Fabiato (1975), studies on myocardial function from analysis of single cardiac muscle cells have received an increased attention. Experiments conducted at the isolated cell level enable an analysis of cardiomyocyte response to mechanical stress, as well as a visualisation of fast cytosolic and nuclear calcium dynamics in contracting cardiac myocytes. It is known that mechanical stress induces an increase of intracellular calcium concentrations and different possible transduction mechanisms have been proposed (Ruwhof, 2001). In addition to these cell membrane phenomena, the mechanism of calcium-induced calcium release (CICR) seems also involved (Fabiato, 1983). In this work, we analyse rhythmic cardiomyocytes contractions starting from the CICR model of Goldbeter et al. (1990). In addition, we consider the effect of anisotropic calcium diffusion and propose a mechano-chemical coupling of Ca^{2+} cytosolic concentrations with anisotropic cell sarcomeres contraction. The simulated spatio-temporal cell contractions are validated by comparison with time-lapse videomicroscopic sequences of spontaneously and periodically contracting isolated rat cardiac myocytes.

The mechano-chemical model

The CICR model for calcium oscillations we consider is a modified version of the nonlinear kinetic model of Goldbeter et al. (1990). In order to take into account the propagation of free calcium, we extend this kinetic model by adding a calcium diffusion term which reproduces the anisotropic calcium diffusion observed experimentally. The two-dimensional cell contraction is generated by a calcium dependent active stress tensor σ_{active}. The total intracellular stress σ is thus: $\sigma = \sigma_{passive} + \sigma_{active}$, where $\sigma_{passive}$ is the passive stress. We assume that the passive cell response is linear elastic, while the active stress tensor is anisotropic, due to the sarcomeres spatial arrangement. As a result, the constitutive stress-strain relationship driving cell contraction is given by:

$$\sigma = \frac{E}{(1+\nu)}\left[\varepsilon + \frac{\nu}{(1-2\nu)}\mathrm{Trace}(\varepsilon).\mathbf{I}\right] + \beta(Z).T_0.\mathbf{e}_x \otimes \mathbf{e}_x$$

In this equation, $\mathbf{I}$ is the identity tensor, ε the strain tensor, while E and ν are respectively the elastic modulus and Poisson ratio. The term $\beta(Z(\mathbf{r},t)).T_0$ is the local active tension driven by the intracellular calcium concentration at spatial location $\mathbf{r}$. The vector $\mathbf{e}_x$ refers to the principal cell axis. Neglecting inertial effects and volumic forces, the local mechanical equilibrium equation reads $\nabla.\sigma = \mathbf{0}$.

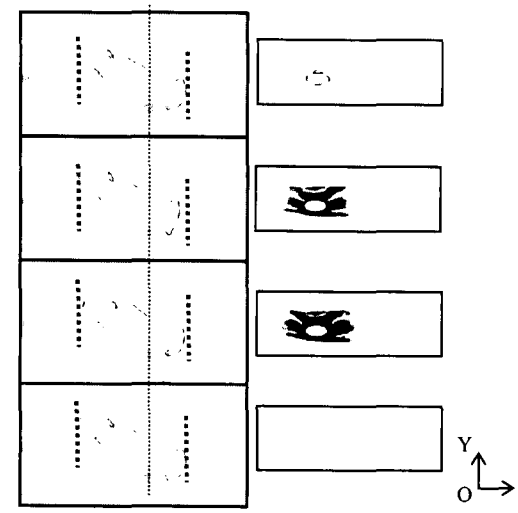

Fig. 2. Left: Time-lapse sequence of an isolated rat cardiomyocyte shown at successive times. Top to bottom: t_d=0s, t_1=0,6s, t_2 =1s and t_3 =1,5s, (t_d is the beginning of a contraction). Right: spatial principal stress distribution σ_{xx}. Top to bottom: t_d=0s and σ^{max}_{xx}=0,1kPa; t'_1=0,5s.

Results and discussion

Fig. 1 shows that, for kinetic and mechanical parameters values coherent with experimental data, the simulated cardiomyocyte contraction compares very satisfactorily with the observed real cell morphological changes: the simulated contraction period is close to 1.5s, while the contraction amplitude is in the order of 13µm. Maximum stresses are obtained in the central cell region, as expected from the centripetal cell contraction. In conclusion, we propose a rather simple integrative model of cardiomyocyte oscillating contraction which appears as a reliable basis for further investigation of the different mechano-transduction pathways where calcium dynamics are modulated by mechanical intracellular or membranous strains.

References

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